Remarks

The Office Action mailed May 27, 2003, has been received and reviewed. Claims 89-97, 104, 105 and 120-122 having been amended, and claims 123-128 having been added, the pending claims are claims 1 and 61-128. Of these, claims 61-88, 98-103 and 106-119 have been withdrawn from consideration by the Examiner, such that claims 89-97, 104, 105 and 120-128 are presently under examination. Reconsideration and withdrawal of the rejections are respectfully requested.

Independent claims 89, 104, 105 and 120-122 have been amended to recite a non-naturally occurring polypeptide, and claims 89, 104 and 105 have been further amended to recite a bioactive peptide having the recited stabilizing groups attached to its N- and C-termini. Support for the claim amendments can be found throughout the specification including, for example, at page 17, lines 30-34, page 22, lines 12-30, and page 27, lines 3-17. New claims 123-128, reciting a naturally occurring bioactive peptide, are supported by the specification at, for example, page 22, lines 12-30. No new matter has been introduced.

Applicant notes that neither the Office Action nor the Office Action Summary indicates the Examiner's disposition of claim 1. Since this claim was included in unelected Group I, Applicant will proceed under the assumption that claim 1 has been withdrawn from consideration by the Examiner. The Examiner is asked to clarify the disposition of claim 1 in the next Official Communication. Although the Applicant is treating this claim as if it were withdrawn from consideration, it is identified above in the "Listing of claims" as a "previously presented" claim pending clarification from the Examiner.

Applicant respectfully requests reconsideration of claims 89-97, 104, 105 and 120-122, and allowance of these claims as well as newly added claims 123-128 in view of the above amendments and following remarks.

Information Disclosure Statements

A copy of the 1449 Form mailed December 5, 2000, and a copy of the return-stamped postcard are submitted herewith **(Exhibit A)**, however, Applicant's Representatives have not received an initialed copy indicating that the documents listed thereon have been considered by the Examiner.

A copy of the 1449 Form mailed February 9, 2001, and a copy of the return-stamped postcard are submitted herewith **(Exhibit B)**, however, Applicant's Representatives have not received an initialed copy indicating that the documents listed thereon have been considered by the Examiner.

A copy of the 1449 Form mailed July 31, 2002, and a copy of the return-stamped postcard are submitted herewith **(Exhibit C)**, however, the initialed copy of the 1449 Form returned to Applicant's Representatives does not indicate that the foreign and non-patent documents listed thereon have been considered by the Examiner.

A copy of the 1449 Form mailed May 8, 2003, and a copy of the return-stamped postcard are submitted herewith **(Exhibit D)**, however, Applicant's Representatives have not received an initialed copy indicating that the documents listed thereon have been considered by the Examiner.

In a telephone conversation with Applicant's Representatives on August 20, 2003, the Examiner indicated that copies of the documents sent with the above mentioned Information Disclosure Statements could not be located at the U.S. Patent and Trademark Office.

To assist the Examiner, replacement copies of all documents listed on the 1449 forms indicated above are provided herewith, as well as clean copies (**Exhibits A-D**) of the associated 1449 forms. Applicant requests that the Examiner consider these documents and provide an initialed copy of the 1449 forms indicating consideration of this art with the next Official Communication.

Objections to Specification/Claims

The Examiner objected to the application for not containing an abstract of the disclosure as required by 37 C.F.R. §1.72(b). However, the application as filed did contain an abstract of the disclosure. This abstract was published on the front page of WO 00/22112. For the Examiner's convenience, a copy of the abstract as originally filed in the international application is included as **Exhibit E.** The Examiner is requested to withdraw this objection.

The Examiner indicated that "PCR," "CAP," and "ori" should be spelled out in the first instance of use. The specification has been amended at page 45, line 1, to recite "polymerase chain reaction." The specification has been amended at page 9, line 18 to recite "catabolite gene activator protein." The specification has been amended at page 9, line 32, to recite "origin of replication." The Examiner is requested to withdraw this objection.

The Examiner asserted that on page 43, line 4, "5 OD_{550}" does not "unambiguously identify the cell equivalents to which the phrase precedes." The specification has been amended to recite that 0.1 ml aliquots of cells at an OD_{550} were transduced. Withdrawal of the objection is requested.

Rejection under 35 U.S.C. §101

The Examiner rejected claims 89-97, 104-115, and 120-122 under 35 U.S.C. §101 for being directed to non-statutory subject matter. This rejection is respectfully traversed.

In rejecting the claims under 35 U.S.C. §101, the Examiner asserted that claims 89 (and claims dependent therefrom), 104, 105 and 120-122, as written, "do not distinguish the claimed peptides or polypeptides from naturally existing products." In particular, the Examiner asserts that US Pat. No. 5,633,229 teaches, at Fig. 3, a naturally occurring antimicrobial peptide, termed "Proph1", which has the stabilizing group "Xaa-Pro-Pro".

A careful review of Fig. 3 shows that the amino acid sequence for prophenin-1 (proph1) begins with the sequence Ala-Phe-Pro-Pro- (the "A" is in the upper left hand corner; see also SEQ ID NO:1 in the Sequence Listing at cols. 15-16). Ala-Phe-Pro-Pro- is an embodiment of the generic sequence Xaa-Xaa-Pro-Pro, not Xaa-Pro-Pro as recited in claims 89, 104, 105 and 120-122. None of the pending claims read on the naturally occurring peptide prophenin-1.

Although it is the Applicant's position that the Examiner has failed to provide evidence of a bioactive peptide present in its natural environment (i.e., unaffected by the hand of man) that falls within the scope of any of the pending claims, in order to facilitate prosecution of the above-identified application independent claims 89, 104, 105, and 120-122 have been amended to recite a non-naturally occurring polypeptide. Reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §101 is, accordingly, requested.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 89-97, 104-105, and 120-122 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner asserted that the phrase "stabilizing group" is unclear. This rejection is respectfully traversed.
The specification indicates that stabilizing groups enhance the stability of bioactive

peptides in the intracellular environment. See page 20, line 27 through page 21, line 19 of the specification. Thus, the term "stabilizing group" is sufficiently definite. The Examiner is requested to withdraw the rejection under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §102

The Examiner rejected claims 89 and 97 under 35 U.S.C. §102(b) as being anticipated by Vanhoof et al. (FASEB J. (1995) 9:736-744). The Examiner asserted that the Vanhoof et al. reference discloses Neuropeptide Y, a bioactive peptide that has a stabilizing group "Tyr-Pro" at the N-terminus and a "Pro-Ala" at the C-terminus. This rejection is respectfully traversed.

Neuropeptide Y does not contain a "Pro-Ala" at the C-terminus, nor does it contain at the C-terminus any other stabilizing group recited in claim 89. Shimizu et al. teach that Neuropeptide Y is an amidated peptide of 36 amino acids (Shimizu et al., pg. 2745, first column). Neuropeptide Y is proline rich, containing four prolines at positions 2, 5, 8 and 13. There are no additional peptides after position 13. The C-terminus of Neuropeptide Y is Q-R-H-NH_2 (it is amidated).

Table 4 in Vanhoof et al., entitled "Proline-containing neuro-and vasoactive peptides in human," shows only a partial sequence (i.e., the first 14 amino acids) for Neuropeptide Y, which is just long enough to illustrate the four prolines in the sequence. As the partial sequence for Neuropeptide Y taught in Vanhoof et al. does not include the C-terminus, Vanhoof et al. do not anticipate present claims 89 and 97. The Examiner is requested to withdraw the rejection under 35 U.S.C. §102(b).

The Examiner rejected claims 89, 91, 96, 97, and 120 under 35 U.S.C. §102(a) as being anticipated by Kokryakov et al. (U.S. Patent No. 5,804,553). This rejection is respectfully traversed.

The Examiner asserted that the Kokryakov patent teaches an antibiotic bioactive peptide (FPPPNFPGPR) that contains a plurality of proline residues at the N-

and C-termini of the peptide. This sequence is cited as anticipating claims 89, 96, 97 and 120.

The Examiner asserted that Kokryakov et al. teaches a bioactive peptide having the sequence of SEQ ID NO:9 which contains an "Xaa-Pro-Pro" motif at the N-terminus and a "Pro-Pro-Xaa" motif at the C-terminus, which allegedly anticipates claims 89 and 91.

Applicant responds by noting to begin with that claim 91 recites that the first stabilizing group is Pro-Pro- and the second stabilizing group is –Pro-Pro. The Kokryakov peptides cited above do not have this motif and therefore do not anticipate claim 91.

Further, the Examiner is requested to note that claims 89 and 120 as amended herewith, are now directed to a non-naturally occurring polypeptide comprising a bioactive peptide to which a stabilizing group, as recited in the respective claims, has been attached at either (claim 120) or both (claim 89) of the N-terminus or C-terminus of the bioactive peptide.

The proline residues in the peptides taught in Kokryakov et al. are part of the bioactive peptide as it naturally occurs. Kokryakov et al. do not teach or suggest a non-naturally occurring polypeptide comprising a bioactive peptide to which a stabilizing group, as recited in the claim, has been attached at either or both of the N-terminus or C-terminus of the bioactive peptide. Thus, the Kokryakov et al. patent does not anticipate present claims 89, 91, 96-97, and 120. The Examiner is requested to withdraw the rejection under 35 U.S.C. §102(a).

With respect to the Examiner's comments that the antibiotic peptide of Kokryakov meets the limitation of claim 120, we note for the record that present claim 120 is not limited to antibiotic peptides.

The Examiner rejected claims 89, 90, 92 and 104 under 35 U.S.C. §102(e) as being anticipated by Hanafusa et al. (U.S. Patent No. 5,888,763). This rejection is respectfully traversed.

The Examiner characterized the Hanafusa patent as disclosing a bioactive peptide (PPPALPPKKN; SEQ ID NO:26 in Hanafusa et al.) having an N-terminal proline residue in comparison with the consensus sequence (PPALPPKKN; SEQ ID NO:27 in Hanafusa et al.). From this the Examiner concludes that the reference meets the limitation set forth in claim 89 that the stabilizing group is selected from the groups recited therein. Applicant disagrees.

Claim 89, as amended, is directed to a polypeptide comprising a bioactive peptide, a first stabilizing group attached to the N-terminus of the bioactive peptide, and a second stabilizing group attached to the C-terminus of the bioactive peptide. The peptides cited by the Examiner do not contain a stabilizing group at the C-terminus. The Hanafusa et al. patent thus does not anticipate claim 89.

The Examiner further asserted that the bioactive peptide was fused to glutathione sulfotransferase (GST), a small stable protein, and that the fusion protein is a substrate for proteolytic cleavage, therefore anticipating claims 89, 90, 92 and 104 of the instant application. Applicant again disagrees.

Claims 89, 90, 92 and 104 recite first (N-terminus) and second (C-terminus) stabilizing groups. The GST fusion protein taught in Hanafusa et al. is an N-terminal fusion (i.e., the link between GST and the peptide is between the C-terminus of GST and the N-terminus or the peptide). See, for example, the recitation of gst-CB-1, gst-CB-2, gst-CB-3 and gst-CB-4 at col. 30, lines 58-59. The proline motif of SEQ ID NOs: 26 and 27 in Hanafusa et al., however, is also at the N-terminus of the peptide. The fusion protein taught in Hanafusa et al. thus does not contain a stabilizing group at the C-terminus. The GST fusion protein taught in Hanafusa et al. therefore does not anticipate claim 89, 90, 92 or 104.

It is thus respectfully submitted that the Hanafusa et al. patent does not anticipate claims 89, 90, 92 and 104. The Examiner is requested to withdraw the rejection under 35 U.S.C. §102(e).

Rejections under 35 U.S.C. 103(a)

The Examiner rejected claims 89, 96 and 97 under 35 U.S.C. §103(a) as being obvious over Vanhoof et al. in view of Shimizu et al. (Antimicrob. Agents Chemother. (1998) 42:2745-2746). This rejection is respectfully traversed.

The Examiner asserted that the Vanhoof et al. reference teaches bioactive neuropeptides that "hinder proteolysis and have stabilized bioactivity" and that have a "Tyr-Pro" stabilizing group at the N-terminus and a "Pro-Ala" stabilizing group at the C-terminus of Neuropeptide Y. The Examiner asserted that the Shimizu et al. reference teaches that Neuropeptide Y has antimicrobial activity. The Examiner asserted that "it would have been obvious for the ordinary skilled artisan to combine the above references to successfully arrive at the invention set forth in the application claims 89, 96 and 97 as to the therapeutic peptide drug and antimicrobial peptide agent." Applicant respectfully disagrees.

Claim 89, as amended, is directed to a polypeptide comprising a bioactive peptide, a first stabilizing group attached to the N-terminus of the bioactive peptide, and a second stabilizing group attached to the C-terminus of the bioactive peptide. As noted above in connection with the rejection under 35 U.S.C. §102(b), the sequence of Neuropeptide Y taught in Vanhoof et al. is a partial sequence and does not contain a C-terminus. Neither Vanhoof et al., nor the secondary reference Shimizu et al, teach or suggest a second stabilizing group at the C-terminus of a peptide. The combination of references therefore does not teach all the elements of claim 89 (and claims dependent therefrom). The Examiner is requested to withdraw the rejection of claims 89, 96 and 97 under 35 U.S.C. §103 (a) as being obvious over Vanhoof et al. in view of Shimizu et al. (Antimicrob. Agents Chemother. (1998) 42:2745-2746).

The Examiner rejected claims 89, 90, 92-94 and 104 under 35 U.S.C. §103 as being obvious over the Hanafusa patent in view of Nishida et al. (J. Mol. Biol. (1998)

281:135-147); Weiss et al. (J. Virol. (1995) 69:4776-4783); and Spurlino et al. (J. Biol. Chem. (1991) 266:5202-5219). This rejection is respectfully traversed.

Claims 89 and 104, as amended, recite a polypeptide comprising a bioactive peptide, a first stabilizing group attached to the N-terminus of the bioactive peptide, and a second stabilizing group attached to the C-terminus of the bioactive peptide. As noted above in connection with the rejection under 35 U.S.C. §102(e), neither SEQ ID NOs: 26 or 27 nor the fusion protein taught in Hanafusa et al. contains a stabilizing group at the C-terminus. This deficiency is not remedied by the secondary references cited (Nishida et al., teaching the crystal structure of GST; Weiss et al., teaching a GST-peptide fusion protein; and Spurlino et al, teaching the crystal structure of maltose binding protein). As a result, the combination of references does not teach all the elements of claims 89, 90, 92-94, and 104. The Examiner is requested to withdraw the rejection of claims 89, 90, 92-94, and 104 under 35 U.S.C. §103 as being obvious over the Hanafusa patent in view of Nishida et al. (J. Mol. Biol. (1998) 281:135-147); Weiss et al. (J. Virol. (1995) 69:4776-4783); and Spurlino et al. (J. Biol. Chem. (1991) 266:5202-5219).

Summary

It is respectfully submitted that claims 89-97, 104, 105 and 120-128 are in condition for allowance, and notification to that effect is respectfully requested. The Examiner is invited to contact Applicant's Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Elliot Altman

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

Aug 22, 2003
Date

By: _____
Victoria A. Sandberg
Reg. No. 41,287
Direct Dial (612)305-1226

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV 073 736 048 US Date of Deposit: 22 AUGUST 2003
The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents,P.O. Box 1450, Alexandria, VA 22313-1450.

By: _____
Name: JILL R. AGUILAR